HFA-305

Date of Approval: FEB 27 2004

FREEDOM OF INFORMATION SUMMARY

NADA 140-338

NAXCEL Sterile Powder

Ceftiofur sodium

This supplement updates survey microbiological data and adds NCCLS interpretive criteria for equine isolates to the NAXCEL Sterile Powder package insert

Sponsored by:

Pharmacia & Upjohn Co.

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1. GENERAL INFORMATION:

a.	File Number:	NADA 140-338
b.	Sponsor:	Pharmacia & Upjohn Co. 7000 Portage Road Kalamazoo, MI 49001-0199 Drug Labeler Code: 000009
c.	Established Name:	ceftiofur sodium
d.	Proprietary Name:	NAXCEL Sterile Powder
e.	Dosage Form:	Injectable
f.	How Supplied:	1 gram and 4 gram vials
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	Each mL of reconstituted solution contains ceftiofur sodium equivalent to 50 mg ceftiofur
i.	Route of Administration:	Intramuscular and subcutaneous injections
j.	Species/Class:	Cattle, swine, sheep, goats, dogs, horses, day-old chickens, and day-old turkey poults
k.	Recommended Dosage:	Horse: 1 to 2 mg/lb body weight IM only (relevant to current submission)
l.	Pharmacological Category:	antimicrobial
m.	Indications:	**Horse:** NAXCEL Sterile Powder is indicated for the treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus.* (relevant to current submission)
n.	Effect of Supplement:	This supplement updates survey microbiological data and adds the National Committee for Clinical Laboratory Standards' (NCCLS) interpretive criteria for equine isolates to the NAXCEL Sterile Powder package insert.

2. *EFFECTIVENESS:*

Table 2 of the package insert for NAXCEL Sterile Powder presents bacterial isolates collected over time from diagnostic laboratories in the US and Canada in tabular format. In the revised package insert, updated *in vitro* minimum inhibitory concentration (MIC) data for equine respiratory pathogens have been added to Table 2.

Table 2. Ceftiofur MIC values of bacterial isolates from diagnostic laboratories* in the USA and Canada

Animal	Organism	Number Tested	Date Tested	MIC_{90}** (µg/mL)	MIC Range (µg/mL)
Bovine	*Mannheimia haemolytica*	110	1997-1998	0.06	≤ 0.03-0.25
	Mannheimia haemolytica	139	1998-1999	≤ 0.03	≤ 0.03-0.5
	Mannheimia haemolytica	209	1999-2000	≤ 0.03	≤ 0.03-0.12
	Mannheimia haemolytica	189	2000-2001	≤ 0.03	≤ 0.03-0.12
	Pasteurella multocida	107	1997-1998	≤ 0.03	≤ 0.03-0.25
	Pasteurella multocida	181	1998-1999	≤ 0.03	≤ 0.03-0.5
	Pasteurella multocida	208	1999-2000	≤ 0.03	≤ 0.03-0.12
	Pasteurella multocida	259	2000-2001	≤ 0.03	≤ 0.03-0.12
	Haemophilus somnus	48	1997-1998	≤ 0.03	≤ 0.03-0.25
	Haemophilus somnus	87	1998-1999	≤ 0.03	≤ 0.03-0.125
	Haemophilus somnus	77	1999-2000	≤ 0.03	≤ 0.03-0.06
	Haemophilus somnus	129	2000-2001	≤ 0.03	≤ 0.03-0.12
	Bacteroides fragilis group	29	1994	16.0	≤ 0.06->16.0
	Bacteroides spp., non-fragilis group	12	1994	16.0	0.13->16.0
	Peptostreptococcus anaerobius	12	1994	2.0	0.13-2.0
Swine	*Actinobacillus pleuropneumoniae*	97	1997-1998	≤ 0.03	no range
	Actinobacillus pleuropneumoniae	111	1998-1999	≤ 0.03	≤ 0.03-0.25
	Actinobacillus pleuropneumoniae	126	1999-2000	≤ 0.03	≤ 0.03-0.06
	Actinobacillus pleuropneumoniae	89	2000-2001	≤ 0.03	≤ 0.03-0.06
	Pasteurella multocida	114	1997-1998	≤ 0.03	≤ 0.03-1.0
	Pasteurella multocida	147	1998-1999	≤ 0.03	≤ 0.03-0.5
	Pasteurella multocida	173	1999-2000	≤ 0.03	≤ 0.03-0.06
	Pasteurella multocida	186	2000-2001	≤ 0.03	≤ 0.03-0.12
	Streptococcus suis	106	1997-1998	0.5	≤ 0.03-4.0
	Streptococcus suis	142	1998-1999	0.25	≤ 0.03-1.0
	Streptococcus suis	146	1999-2000	0.06	≤ 0.03-4.0
	Streptococcus suis	167	2000-2001	0.06	≤ 0.03-4.0
	Salmonella choleraesuis	96	1999-2000	1.0	0.03->4.0
	Salmonella choleraesuis	101	2000-2001	1.0	0.5-2.0
	Erysipelothrix rhusiopathiae	44	2002	≤ 0.03	≤ 0.03-0.06
Equine	*Streptococcus equi* subsp. *equi*	12	1994	≤ 0.0019	no range
	Streptococcus equi subsp. *equi*	29	2002	≤ 0.03	≤ 0.03-0.05
	Streptococcus zooepidemicus	48	1994	≤ 0.0019	no range

	Streptococcus zooepidemicus	59	2002	≤ 0.03	≤ 0.03-0.25
	Rhodococcus equi	66	1998	4.0	≤ 0.03-16.0
	Rhodococcus equi	42	2002	8.0	≤ 0.03->32.0
	Bacteroides fragilis group	32	1995	> 16.0	0.13-> 16.0
	Bacteroides spp., non-fragilis group	12	1995	4.0	0.25-4.0
	Fusobacterium necrophorum	16	1995	≤ 0.06	no range
Canine	*Escherichia coli*	26	2000	32	0.25->32
	Proteus mirabilis	14	2000	0.25	0.06-0.25
Turkey	*Escherichia coli*	17	1998-1999	1.0	0.25-1.0
	Escherichia coli	25	1999-2000	0.50	0.12-0.50
	Escherichia coli	20	2000-2001	2.0	0.12-16
	Citrobacter spp.	37	1995	32.0	0.5->32.0
	Enterobacter spp.	51	1995	> 32.0	0.13->32.0
	Klebsiella spp.	100	1995	1.0	0.13-2.0
	Proteus spp.	19	1995	1.0	0.06-32.0
	*Pseudomonas spp.****	31	1995	> 32.0	0.06->32.0
	Salmonella spp.	24	1995	1.0	0.5-1.0
	Staphylococcus spp. (coagulase-positive)	17	1995	2	1.0-2.0
	Staphylococcus spp. (coagulase-negative)	26	1995	8	0.13->32.0
Chicken	*Escherichia coli*	62	1997-1998	0.50	0.25-2.0
	Escherichia coli	53	1998-1999	4.0	0.25->4
	Escherichia coli	67	1999-2000	0.50	0.12-16
	Escherichia coli	90	2000-2001	1.0	< 0.03-8

*The following *in vitro* data are available but their clinical significance is unknown.
**Minimum inhibitory concentration (MIC) for 90% of the isolates.
***MIC_{50} is 32 µg/mL

The interpretive criteria for equine isolates have been added to the package insert. The interpretive criteria for ceftiofur are described below Table 2 in the package insert as follows:

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) body weight (swine) or 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data, the following breakpoints are recommended by NCCLS.

Zone diameter (mm)	**MIC (µg/mL)**	**Interpretation**
≥ 21	≤ 2.0	(S) Susceptible
18-20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if infection is in a body site where the drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Based on the pharmacokinetic studies of ceftiofur in horses after a single intramuscular injection of 1 mg ceftiofur equivalents/lb (2.2 mg/kg) BW, clinical effectiveness data and MIC data, the following breakpoint is recommended by NCCLS.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 22	≤ 0.25	(S) Susceptible

The susceptible only category is used for populations of organisms (usually one species) for which regression analysis (disk vs. MIC) cannot be performed. These breakpoints will permit detection of strains with decreased susceptibility as compared to the original population.

3. TARGET ANIMAL SAFETY:

This supplement to NADA 140-338 does not change the target animal safety data for this product.

4. HUMAN SAFETY:

This supplement to NADA 140-338 does not change the human safety data for this product.

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data provide updated equine clinical microbiology information and NCCLS interpretive criteria for use by veterinarians to assist them in making sound therapeutic decisions for the use of NAXCEL Sterile Powder in the horse.

The product remains restricted to use by or on the order of a licensed veterinarian because professional expertise is needed for the diagnosis and treatment of diseases in cattle, swine, sheep, goats, dogs, horses, day-old chickens, and day-old turkey poults.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

6. ***ATTACHMENTS:***

Facsimile labeling is attached as indicated below:

Package insert

Naxcel®

brand of ceftiofur sodium sterile powder

Pharmacia & Upjohn

For intramuscular and subcutaneous injection in cattle only. For intramuscular injection in swine, sheep, goats, and horses. For subcutaneous injection only in dogs, day-old chickens and day-old turkey poults. This product may be used in lactating dairy cattle, sheep, and goats.

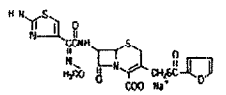
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

NAXCEL Sterile Powder contains the sodium salt of ceftiofur which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal *in vitro*, resulting from inhibition of cell wall synthesis.

Each mL of the reconstituted drug contains ceftiofur sodium equivalent to 50 mg ceftiofur. The pH was adjusted with sodium hydroxide and monobasic potassium phosphate.

Chemical Structure of Ceftiofur Sodium



Chemical Name of Ceftiofur Sodium

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[(2-furanylcarbonyl) thio] methyl]-8-oxo-, monosodium salt, [6R-[6α,7β (Z)]]-

RECONSTITUTION OF THE STERILE POWDER

NAXCEL Sterile Powder should be reconstituted as follows.

1 gram vial—Reconstitute with 20 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

4 gram vial—Reconstitute with 80 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

STORAGE CONDITIONS

Store **unreconstituted** product at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

Store **reconstituted** product either in a refrigerator 2° to 8° C (36° to 46° F) for up to 7 days or at controlled room temperature 20° to 25° C (68° to 77° F) [see USP] for up to 12 hours.

Protect from light. Color of the cake may vary from off-white to a tan color. Color does not affect potency.

ONE-TIME SALVAGE PROCEDURE FOR RECONSTITUTED PRODUCT

At the end of the 7-day refrigeration or 12-hour room temperature storage period following reconstitution, any remaining reconstituted product may be frozen for up to 8 weeks without loss in potency or other chemical properties. This is a one-time only salvage procedure for the remaining product. To use this salvaged product at any time during the 8-week storage period, hold the vial under warm running water, gently swirling the container to accelerate thawing, or allow the frozen material to thaw at room temperature. Rapid freezing or thawing may result in vial breakage. Any product not used immediately upon thawing should be discarded.

CLINICAL MICROBIOLOGY

Summaries of MIC data are presented in Tables 1 and 2. Testing followed NCCLS Guidelines (National Committee for Clinical Laboratory Standards).

Table 1. Ceftiofur MIC Values of Bacterial Isolates from Clinical Field Studies in the USA

Animal	Organism	Number Tested	Date Tested	MIC_{90}* (µg/mL)	MIC Range (µg/mL)
Bovine	*Mannheimia haemolytica*	461	1988-1992	0.06	≤0.03-0.13
	Mannheimia haemolytica	42	1993	0.015	≤0.003-0.03
	Pasteurella multocida	318	1988-1992	0.06	≤0.03-0.25
	Pasteurella multocida	48	1993	<0.003	<0.003-0.015
	Haemophilus somnus	109	1988-1992	0.06	≤0.03-0.13
	Haemophilus somnus	59	1993	≤0.0019	no range
	Fusobacterium necrophorum	17	1994	≤0.06	no range
Swine	*Actinobacillus pleuropn.*	83	1993	≤0.03	≤0.03-0.06
	Pasteurella multocida	74	1993	≤0.03	≤0.03-0.06
	Streptococcus suis	94	1993	0.25	≤0.03-1.0
	Salmonella choleraesuis	50	1993	1.0	1.0-2.0
	beta-hemolytic *Streptococcus* spp.	24	1993	≤0.03	≤0.03-0.06
	Actinobacillus suis	77	1998	0.0078	0.0019-0.0078
	Haemophilus parasuis	76	1998	0.06	0.0039-0.25
Sheep	*Mannheimia haemolytica*	39	1992	0.13	≤0.03-0.13
	Pasteurella multocida	23	1992	<0.03	no range
Canine	*Escherichia coli*	44	1992	4.0	0.06-64.0
	Escherichia coli	18	1990	0.25	0.13-0.5
	Proteus mirabilis	17	1990	≤0.06	≤0.06-0.5
	Proteus mirabilis	23	1992	1.0	≤0.06-4.0
Turkey	*Escherichia coli*	1204	1995	1.0	0.13->32.0

*Minimum inhibitory concentration (MIC) for 90% of the isolates.

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Table 2. Ceftiofur MIC Values of Bacterial Isolates from Diagnostic Laboratories in the USA and Canada*

Animal	Organism	Number Tested	Date Tested	MIC_{90}** (µg/mL)	MIC Range (µg/mL)
Bovine	*Mannheimia haemolytica*	110	1997-1998	0.06	≤0.03-0.25
	Mannheimia haemolytica	139	1998-1999	≤0.03	≤0.03-0.5
	Mannheimia haemolytica	209	1999-2000	<0.03	<0.03-0.12
	Mannheimia haemolytica	189	2000-2001	≤0.03	≤0.03-0.12
	Pasteurella multocida	107	1997-1998	≤0.03	≤0.03-0.25
	Pasteurella multocida	181	1998-1999	≤0.03	≤0.03-0.5
	Pasteurella multocida	208	1999-2000	≤0.03	≤0.03-0.12
	Pasteurella multocida	259	2000-2001	≤0.03	≤0.03-0.12
	Haemophilus somnus	48	1997-1998	≤0.03	≤0.03-0.25
	Haemophilus somnus	87	1998-1999	≤0.03	≤0.03-0.125
	Haemophilus somnus	77	1999-2000	<0.03	<0.03-0.06
	Haemophilus somnus	129	2000-2001	≤0.03	≤0.03-0.12
	Bacteroides fragilis group	29	1994	16.0	≤0.06->16.0
	Bacteroides spp., non-fragilis group	12	1994	16.0	0.13->16.0
	Peptostreptococcus anaerobius	12	1994	2.0	0.13-2.0
Swine	*Actinobacillus pleuropn.*	97	1997-1998	≤0.03	no range
	Actinobacillus pleuropn.	111	1998-1999	≤0.03	≤0.03-0.25
	Actinobacillus pleuropn.	126	1999-2000	≤0.03	≤0.03-0.06
	Actinobacillus pleuropn.	89	2000-2001	≤0.03	≤0.03-0.06
	Pasteurella multocida	114	1997-1998	≤0.03	≤0.03-1.0
	Pasteurella multocida	147	1998-1999	≤0.03	≤0.03-0.5
	Pasteurella multocida	173	1999-2000	≤0.03	≤0.03-0.06
	Pasteurella multocida	186	2000-2001	≤0.03	≤0.03-0.12
	Streptococcus suis	106	1997-1998	0.5	≤0.03-4.0
	Streptococcus suis	142	1998-1999	0.25	≤0.03-1.0
	Streptococcus suis	146	1999-2000	0.06	≤0.03-4.0
	Streptococcus suis	167	2000-2001	0.06	<0.03-4.0
	Salmonella choleraesuis	96	1999-2000	1.0	0.03->4.0
	Salmonella choleraesuis	101	2000-2001	1.0	0.5-2.0
	Erysipelothrix rhusiopathiae	44	2002	≤0.03	≤0.03-0.06
Equine	*Streptococcus equi subsp. equi*	12	1994	≤0.0019	no range
	Streptococcus equi subsp. equi	29	2002	≤0.03	≤0.03-0.05
	Streptococcus zooepidemicus	48	1994	≤0.0019	no range
	Streptococcus zooepidemicus	59	2002	<0.03	<0.03-0.25
	Rhodococcus equi	66	1998	4.0	≤0.03-16.0
	Rhodococcus equi	42	2002	8.0	≤0.03->32.0
	Bacteroides fragilis group	32	1995	>16.0	0.13->16.0
	Bacteroides spp. non-fragilis group	12	1995	4.0	0.25-4.0
	Fusobacterium necrophorum	16	1995	≤0.06	no range
Canine	*Escherichia coli*	26	2000	32	0.25->32
	Proteus mirabilis	14	2000	0.25	0.06-0.25
Turkey	*Escherichia coli*	17	1998-1999	1.0	0.25-1.0
	Escherichia coli	25	1999-2000	0.50	0.12-0.5
	Escherichia coli	20	2000-2001	2.0	0.12-16.0
	Citrobacter spp.	37	1995	32.0	0.5->32.0
	Enterobacter spp.	51	1995	>32.0	0.13->32.0
	Klebsiella spp.	100	1995	1.0	0.13-2.0
	Proteus spp.	19	1995	1.0	0.06-32.0
	Pseudomonas spp.***	31	1995	>32.0	0.06->32.0
	Salmonella spp.	24	1995	1.0	0.5-1.0
	Staphylococcus spp. (coagulase positive)	17	1995	2.0	1.0-2.0
	Staphylococcus spp. (coagulase negative)	26	1995	8.0	0.13->32.0

(continued)

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Animal	Organism	Number Tested	Date Tested	MIC_{90}** (µg/mL)	MIC Range (µg/mL)
Chicken	*Escherichia coli*	62	1997-1998	0.50	0.25-2.0
	Escherichia coli	53	1998-1999	4.0	0.25->4.0
	Escherichia coli	67	1999-2000	0.50	0.12-16.0
	Escherichia coli	90	2000-2001	1.0	≤0.03-8.0

* The following *in vitro* data are available but their clinical significance is unknown.
** Minimum inhibitory concentration (MIC) for 90% of the isolates.
*** MIC_{50} is 32 µg/mL

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (swine) or 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data, the following breakpoints are recommended by NCCLS.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 2.0	(S) Susceptible
18-20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Based on the pharmacokinetic studies of ceftiofur in horses after a single intramuscular injection of 1 mg ceftiofur equivalents/lb (2.2 mg/kg) BW, clinical effectiveness data and MIC data, the following breakpoint is recommended by NCCLS.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 22	≤ 0.25	(S) Susceptible

The susceptible only category is used for populations of organisms (usually one species) for which regression analysis (disk vs. MIC) cannot be performed. These breakpoints will permit detection of strains with decreased susceptibility as compared to the original population.

Standardized procedures[1] require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain. Ceftiofur sodium disks or powder reference standard is appropriate for both ceftiofur salts.

Table 3. Acceptable quality control ranges for ceftiofur against National Committee for Clinical Laboratory Standards recommended American Type Culture Collection (ATCC) reference strains

Organism Name (ATCC Number)	Zone Diameter* (mm)	MIC Range (µg/mL)
Escherichia coli (25922)	26–31	0.25–1.0
Staphylococcus aureus (29213)	—	0.25–1.0
Staphylococcus aureus (25923)	27–31	—
Pseudomonas aeruginosa (27853)	14–18	16.0–64.0
Actinobacillus pleuropneumoniae (27090)	34–42**	0.004–0.015***
Haemophilus somnus (700025)	36–46**	0.0005–0.004***

* All testing performed using a 30µg disk.
** Quality control ranges are applicable only to tests performed by disk diffusion test using a chocolate Mueller-Hinton agar, incubated in 5-7% CO_2 for 20-24 hours.
*** MIC quality control ranges are applicable only to tests performed by broth microdilution procedures using veterinary fastidious medium (VFM).

CATTLE USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Haemophilus somnus*. NAXCEL Sterile Powder is also indicated for treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

Dosage and Administration

Administer to cattle at the dosage of 0.5 to 1.0 mg ceftiofur per pound of body weight (1-2 mL reconstituted sterile solution per 100 lb body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgment of severity of disease (i.e., for respiratory disease, extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite; and for foot rot, extent of swelling, lesion and severity of lameness).

Animal Safety

Results from a five-day tolerance study in normal feeder calves indicated that formulated ceftiofur was well tolerated at 25 times (25 mg/lb/day) the highest recommended dose of 1.0 mg/lb/day for five consecutive days. Ceftiofur administered intramuscularly had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were intramuscularly administered formulated ceftiofur at 0 (vehicle control), 1, 3, 5 and 10 times the highest recommended dose of 1.0 mg/lb/day to determine the safety factor. There were no adverse systemic effects indicating that the formulated ceftiofur has a wide margin of safety when injected intramuscularly into the feeder calves at 10 times (10 mg/lb/day) the recommended dose for three times (15 days) the recommended three to five days of therapy. The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at 1 and 3 times the highest recommended dose of 1.0 mg/lb/day. The histopathological evaluations were conducted at posttreatment days 1, 3, 7 and 14.

The injection of NAXCEL® Sterile Powder at the recommended dose administered SC in the neck of cattle was well tolerated. However, a several square centimeter area of yellow-red discoloration resulting from a single SC injection persisted in many of the cattle beyond 4.5 days post-injection. Also, one of the animals developed an abscess at the injection site.

Residue Warnings: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.

Precautions

Following subcutaneous administration of ceftiofur sodium in the neck, small areas of discoloration at the site may persist beyond five days, potentially resulting in trim loss of edible tissues at slaughter.

As with any parenteral injection, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

SWINE USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* type 2.

Dosage and Administration

Administer to swine at a dosage of 1.36 to 2.27 mg ceftiofur/lb (3.0 to 5.0 mg/kg) of body weight (1 mL of reconstituted sterile solution 22 to 37 pounds of body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days.

Animal Safety

Results from a five-day tolerance study in normal feeder pigs indicated that formulated ceftiofur was well tolerated when administered at 57 mg/lb (more than 25 times the highest recommended daily dosage of 2.27 mg/lb of body weight) for five consecutive days. Ceftiofur administered intramuscularly to pigs produced no overt adverse signs of toxicity.

To determine the safety factor and to measure the muscle irritancy potential in swine, a safety/toxicity study was conducted. Five barrows and five gilts per group were intramuscularly administered formulated ceftiofur at 0, 2.27, 6.81 and 11.36 mg/lb of body weight for 15 days which is 0, 1, 3 and 5 times the highest recommended dose of 2.27 mg/lb of body weight/day and 5 times the recommended treatment length of 3 days. There were no adverse systemic effects indicating that formulated ceftiofur has a wide margin of safety when injected intramuscularly into feeder pigs at the highest recommended dose of 2.27 mg/lb/day for 3 days or at levels up to 5 times the highest recommended dose for 5 times the recommended length of treatment. The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at posttreatment days 1, 2, 3 and 4. By day 10 post injection the muscle reaction was subsiding and at day 15 post injection there was little evidence of muscle damage in any of the pigs in any of the treatment groups.

Residue Warnings: No pre-slaughter drug withdrawal interval is required when using this product according to label indications, dosage, and route of administration. Use of dosages in excess of those indicated or by unapproved routes may result in illegal residues in edible tissues.

Precautions

The safety of ceftiofur has not been determined for swine intended for breeding.

SHEEP USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment of sheep respiratory disease (sheep pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Dosage and Administration

Administer to sheep at the dosage of 0.5 to 1.0 mg ceftiofur per pound of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite).

Animal Safety

In a 15-day safety/toxicity study in sheep, three wether and three ewe lambs per group were given formulated ceftiofur sodium by the intramuscular route 0 (sterile water vehicle), 1, 3 or 5 times the recommended dose of 1.0 mg/lb/day for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in sheep. Based on examination of injection sites from study days 9, 11, 13 and 15, a low incidence of visual changes and histopathologic findings of mild, reversible inflammation from all groups including the controls indicated that the formulation is a slight muscle irritant.

Residue Warnings: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.

GOAT USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment of caprine respiratory disease (goat pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Dosage and Administration

Administer to goats at the dosage of 0.5 to 1.0 mg ceftiofur per pound of body weight (1–2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss

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of appetite). Pharmacokinetic data indicate that elimination of the drug is more rapid in lactating does. For lactating does, the high end of the dose range is recommended.

Animal Safety

In a 15-day safety-toxicity study 5 lactating does, 5 dry does, and 5 wethers were given formulated ceftiofur by the intramuscular route with 11 mg/kg/day for 15 days. This constitutes 5 times the recommended dose for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in goats.

Residue Warnings: Neither a pre slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.

HORSE USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus*

Dosage and Administration

Administer to horses at a dosage of 1.0 to 2.0 mg ceftiofur per pound of body weight (2–4 mL reconstituted sterile solution per 100 lb body weight). A maximum of 10 mL may be administered per injection site. Treatment should be repeated at 24-hour intervals, continued for 48 hours after clinical signs have disappeared and should not exceed 10 days.

Animal Safety

In a safety study, horses received a daily intramuscular injection of either 0 mg/lb/day (saline control), 1.0 mg/lb/day (50 mg/mL), 3.0 mg/lb/day (100 mg/mL), or 5.0 mg/lb/day (200 mg/mL) of an aqueous solution of ceftiofur sodium for 30 or 31 days. Ceftiofur sodium was well tolerated when administered intramuscularly to male and female horses at doses up to 5.0 mg/lb/day for 30 or 31 days. No clinical evidence of irritation was noted at any dose. The drug-related changes detected in this study were limited to a transient decrease in food consumption in horses receiving 3.0 or 5.0 mg/lb/day ceftiofur, and general mild skeletal muscle irritation at the injection sites which resolved by regeneration of muscle fibers.

In a tolerance study, horses received a single daily intravenous infusion of either 0 (saline), 10.0 or 25.0 mg/lb/day of an aqueous solution (50 mg/mL) of ceftiofur for 10 days. The results indicated that ceftiofur administered intravenously at a dose of 10.0 or 25.0 mg/lb/day apparently can change the bacterial flora of the large intestine thereby leading to inflammation of the large intestine with subsequent diarrhea and other clinical signs (loose feces, eating bedding straw, dehydration, rolling or colic and a dull, inactive demeanor). Decreased food consumption, a loss of body weight, hematologic changes related to acute inflammation and stress, and serum chemistry changes related to decreased food consumption and diarrhea were also associated with treatment at these doses. The adverse effects were most severe a few days after dosing was initiated and tended to become less severe toward the end of the 10-day dosing period.

Residue Warnings: Not for use in horses intended for human consumption.

Precautions

The safety of ceftiofur has not been determined for horses intended for breeding. The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that could be fatal. If acute diarrhea is observed, discontinue use of this antimicrobial and initiate appropriate therapy.

DOG USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for the treatment of canine urinary tract infections associated with *Escherichia coli* and *Proteus mirabilis*.

Dosage and Administration

Administer to dogs by subcutaneous injection at a dosage of 1.0 mg ceftiofur per pound of body weight (0.1 mL reconstituted sterile solution per 5 lbs of body weight). Treatment should be repeated at 24-hour intervals for 5-14 days.

Reconstituted NAXCEL Sterile Powder is to be administered to dogs by subcutaneous injection. No vial closure should be entered more than 20 times. Therefore, only the 1 gram vial is approved for use in dogs.

Animal Safety

Ceftiofur sodium was well tolerated at the therapeutic dose and is safe for the treatment of urinary tract infections in dogs. In the acute safety study, ceftiofur was well tolerated by dogs at the recommended level (1.0 mg/lb) for 5-14 days. When administered subcutaneously for 42 consecutive days, one of four females developed thrombocytopenia (15 days) and anemia (36 days). Thrombocytopenia and anemia also occurred at the 3X and 5X dose levels. In the reversibility phase of the study (5X dose), the thrombocytopenia reversed within 8 days, and of the two anemic animals the male recovered within 6 weeks and the female was sacrificed due to the severity of the anemia.

In the 15-day tolerance study in dogs, high subcutaneous doses (25 and 125 times the recommended therapeutic dose) produced a progressive and dose-related thrombocytopenia, with some dogs also exhibiting anemia and bone marrow changes. The hematopoietic changes noted in dogs treated with ceftiofur were similar to those associated with long-term cephalosporin administration in dogs and also man. The hematopoietic effects are not expected to occur as a result of recommended therapy.

Precautions

The safety of ceftiofur has not been determined for dogs intended for breeding, or pregnant dogs.

DAY-OLD CHICKEN USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old chicks.

Dosage and Administration

Administer by subcutaneous injection in the neck region of day-old chicks at a dosage of 0.08 to 0.20 mg ceftiofur/chick. One mL of the 50 mg/mL reconstituted solution will treat approximately 250 to 625 day-old chicks.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only. A sterile 26 gauge needle and syringe or properly cleaned automatic injection machine should be used.

Animal Safety

In an acute toxicity study of ceftiofur in day-old chicks, a total of 60 male and 60 female chicks were each given single subcutaneous injections of 10, 100 or 1,000 mg/kg of body weight. Treatment on day 1 was followed by 6 days of observation; body weight was determined on days 1, 4 and 7; and selected hematology parameters were evaluated on day 4. No meaningful differences were noted among the treated and control groups of chicks for the parameters evaluated. Histopathologic evaluation of all deaths and chicks surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 20 times (100 mg/kg) the intended highest use dosage.

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DAY-OLD TURKEY POULTS USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old turkey poults.

Dosage and Administration

Administer by subcutaneous injection in the neck region of day-old turkey poults at a dosage of 0.17 to 0.5 mg ceftiofur/poult. One mL of the 50 mg/mL reconstituted solution will treat approximately 100 to 294 day-old turkey poults.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

Animal Safety

In an acute toxicity study of ceftiofur in day-old turkey poults, a total of 30 male and 30 female poults were each administered single subcutaneous injections of 100, 400 or 800 mg/kg body weight. Injection on day 1 was followed by 6 days of observation; body weight on days 1, 4, and 7, and selected hematology parameters on day 4. No meaningful differences were noted between the treated groups at 100 or 400 mg ceftiofur/kg and a negative control group for the parameters evaluated. Histopathologic evaluation of deaths and poults surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 50 times (400 mg/kg) the highest use dosage. A dose of 800 mg/kg (100 times the intended highest use dosage) was toxic, resulting in clinical signs and deaths accompanied by gross and microscopic morphologic tissue alterations.

CONTRAINDICATIONS

As with all drugs, the use of NAXCEL Sterile Powder is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth, and clothing.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information or obtain a material safety data sheet, call 1-800-253-8600.

ADVERSE REACTIONS

The use of ceftiofur may result in some signs of immediate and transient local pain to the animal.

HOW SUPPLIED

NAXCEL Sterile Powder is available in the following package sizes:

1 gram vial	**NDC 0009-3362-03**
4 gram vial	**NDC 0009-3362-04**

[1] National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard – Second Edition. NCCLS document M31-A2. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2002.

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